**OBITUARY FOR PAUL SIGLER**

*by Professors Thomas A. Steitz and Donald M. Engelman*

Dr. Paul Sigler, one of the world's leading structural biologists, died suddenly on Tuesday, January 11, 2000, while walking to his laboratory at Yale University. Sigler was one of the pioneers and one of the giants in structural biology, a field that has provided insights into the amazing chemistry of life. He was Henry Ford II Professor of Molecular Biophysics and Biochemistry at Yale and an Investigator of the Howard Hughes Medical Institute, as well as a member of the U.S. National Academy of Sciences. Although Dr. Sigler was initially trained as a physician at Columbia following his undergraduate education at Princeton University, he turned full-time to a life of basic research after his internship and residency at Columbia-Presbyterian Medical Center. In the early 1960s Sigler joined a very small band of biophysicists who were attempting to unravel the secrets of enzyme function by determining the three-dimensional atomic structure of proteins using X-ray crystallography. After a short time at the Natoinal Institutes of Health, Sigler went to the then Mecca of molecular biology, the Medical Research Council Laboratory in Cambridge, England and joined a group headed by Dr. David Blow; in 1967 they succeeded in solving the atomic structure of the second enzyme to be known. Sigler then spent more than 20 years on the faculty of the University of Chicago, where he established the structure of the RNA molecule involved in the initiation of protein synthesis and began his seminal studies of proteins that regulate the expression of information encoded in genes. He joined the Yale faculty and the Howard Hughes Medical Institute in 1989 to begin what turned out to be the most extraordinarily productive period of his career. At the time of his death Paul Sigler was leading a large and very active laboratory and was widely regarded as one of the preeminent leaders in his field. Paul Sigler's primary focus had been on the chemistry of cellular regulation, focusing on the mechanisms by which gene expression is controlled, transmembrane signaling is accomplished and the way that an enormous protein machine called a chaperonin assists in the correct folding of proteins. His goal in all of these studies was to provide the basis of fundamental biological processes in terms of stereochemistry.

The major scientific contributions of the Sigler laboratory fell in three areas. The most developed of these concerns the regulation of gene expression mediated by proteins that bind specifically to DNA. His studies showed how small molecules, such as steroid hormones, can bind to a protein and alter its structure, thereby altering the protein's affinity for DNA signals at the beginning of a gene and the expression of the information in that gene. These studies have implications for understanding cell development, cancer and hormone regulation. The second area of major scientific contribution by the Sigler lab involves the signal transduction pathway involved in vision. The enzymatic chemical steps that are initiated by light falling on the retina and ending in a signal to the brain are being unraveled at a molecular level, including the mechanism whereby a central protein called a G-protein is regulated as a part of the signaling cascade. Related proteins form an important family of oncogenes. Perhaps among his most stunning technical achievements was the structure determination of a large assembly of protein whose function was to form a machine that assures the correct folding of other newly synthesized proteins into their correct three-dimensional structure. This macromolecular machine is among the largest structures solved and provided unprecedented mechanistic insights into a catalyzed process whose existence was not even known until relatively recently.
Paul Sigler's impact on the field of structural biology far exceeded his own contributions as

enormous as they are.  Beyond his science, he was an exciting and enormous presence, an engaging teller of many stories and a person who befriended and communicated his enthusiasm for science to many all over the world.

Paul Sigler is survived by his wife, Jo, their five children, and a brother.